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(54) **A MEDICAMENT AND METHOD FOR THE PRODUCTION THEREOF**

(57) The present invention can be used in medical practice specifically in chemical and pharmaceutical production of medicinal agents capable of modulating the immune system.

This invention essentially relates to a new medicinal preparation 5-amino-2,3-dihydrophthalazine-1,4-dione sodium salt having immunomodulatory, antiinflammatory, and antioxidant properties.

The preparation is obtained from 3-nitro-phthalanhydride by consecutive isolation of intermediate and end products. The intermediate products include 5-nitro-

2,3-dihydrophthalazine-1,4-dione and 5-amino-2,3-dihydrophthalazine-1,4-dione. The reaction between 5-amino-2,3-dihydrophthalazine-1,4-dione and sodium hydroxide yields the target product, 5-amino-2,3-dihydrophthalazine-1,4-dione sodium salt.

The method allows to produce the medicinal preparation with high pharmaceutical activity.

It is provided an example of application of this preparation.

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Description**FIELD OF THE INVENTION**

- 5 [0001] The present invention relates to the field of medicine, specifically to medicinal preparations affecting the immune system, and to production of such preparations.

BACKGROUND OF THE INVENTION

- 10 [0002] It is known a medicinal preparation "sodium nucleinate" - a sodium salt of nucleic acid - which is an immunological activity preparation, a white or yellowish powder easily soluble in water with formation of opalescent solutions, stimulating migration and cooperation of T-and B-lymphocytes, enhancing phagocytic activity of macrophages, and activity of nonspecific resistance factors (M. D. Mashkovsky, Medicinal Preparations, Meditsina, Moscow (1985), Vol. 2, p. 172 [in Russian]).
- 15 [0003] Injections of this preparation cause, however, pain feeling, which necessitates treatments of patients with analgesics.
- [0004] The closest art for "sodium nucleinate" is 2-amino-1,2,3,4-tetrahydrophthalazine-1,4-dione sodium salt dihydrate, used as an immunomodulator, which also has antiinflammatory and antioxidant properties (Russian Federation Patent No. 21113222, priority: September 30, 1997; IPC: A 61 K 31/04, A 61 K 31/13), being a pale-yellow crystalline
- 20 powder easily soluble in water.
- [0005] Administration of this preparation to patients with impaired cellular immunity, e.g., in case of malignant neoplasms, activates macrophages, interleukins and other acute-phase proteins. In case of inflammatory processes this immunomodulator inactivates macrophages for several hours, but stimulates the microbicidal system in cells.
- [0006] The preparation does not cause side effects and allergic reactions, however, in patients with chronic and other
- 25 diseases long-term treatment with this agent causes tolerance and decreases the efficiency of therapy with this medicinal preparation, which dictates the necessity of substituting other more efficient analogues for the preparation.
- [0007] It is known a method for manufacturing the medicinal preparation including obtaining 3-amino-phthalhydrazide, its molecular rearrangement, followed by treatment with sodium hydroxide, and isolation of the target product of 2-amino-1,2,3,4-tetrahydrophthalazine-1,4-dione sodium salt dihydrate (Russian Federation Patent No. 2138264, Priority; May 6, 1999; IPC: A 61 K 31/50, C 07 D 237/32, Bull. No. 27, September 27, 1999).
- 30 [0008] This method allows to increase the yield of product and decrease the amount of waste products, however, its use is limited to manufacturing of said preparation.
- [0009] The closest art to the present invention is the method for manufacturing 5-amino-2,3-dihydrophthalazine-1,4-dione (luminol) (see e.g., USSR Inventor's Certificate No. 130903, Priority: November 21, 1959; Bull. No. 16, 1960), comprising reduction of 3-nitrophthalic acid with hydrazine hydrate in a water medium in presence of a skeletal nickel
- 35 catalyst, followed by evaporation of the solution, and its heating in presence of hydrazine hydrate and acetic acid at 120°C.
- [0010] The end product of the known method is an orange-colored powder with pronounced luminescence properties, however, this compound is medically ineffective.

SUMMARY OF THE INVENTION

- [0011] The object of the present invention is a medicinal preparation, whose effects is similar, but more pronounced, than those of the closest art thereof, e.g. for replacement of the known preparation in case of patient's tolerance thereto.
- 45 [0012] The present invention the "method for manufacturing the medicinal preparation" is based on development of a procedure providing production of an efficient medicinal preparation, having immunomodulatory, antiinflammatory, and antioxidant properties.
- [0013] The problem was solved by a medicinal preparation 5-amino-2,3-dihydrophthalazine-1,4-dione sodium salt having immunomodulatory, antiinflammatory, and antioxidant properties.
- 50 [0014] This problem was solved by a method for manufacturing 5-amino-2,3-dihydrophthalazine-1,4-dione sodium salt, comprising reduction of the product by hydrazine hydrate in presence of a skeletal nickel catalyst, first by interacting 3-nitro-phthalanhydride with hydrazine hydrate in acetic acid at 90-120°C with formation of 5-nitro-2,3-dihydrophthalazine-1,4-dione, after reduction thereof by hydrazine hydrate in a water-alkaline medium in presence of a skeletal nickel catalyst, isolating 5-amino-2,3-dihydrophthalazine-1,4-dione, which is then treated by sodium hydroxide in the presence of a lower alcohol or a ketone at 20-80°C to obtain the target product.
- 55

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0015] The medicinal preparation is a white or pale-yellow crystalline powder easily soluble in water.

[0016] The medicinal preparation is obtained by the following process:

5 [0017] 3-nitro-phthalanhydride ($C_8H_3NO_6$, 50-60 g) is mixed with acetic acid (CH_3COOH , 120-200 ml) and heated to 90-100°C under mixing with dropwise admixing of hydrazine hydrate ($N_2H_4 \cdot H_2O$, 15-20 ml), maintaining temperature of the reaction mixture at 105-120°C. After addition of hydrazine hydrate, the reaction mass is boiled and held at least 20-45 min and then rapidly cooled to 70-85°C.

10 [0018] Crystallized 5-nitro-2,3-dihydrophthalazine-1,4-dione ($C_8H_5N_3O_4$) is filtered and washed with acetic acid and distilled water. The product (5-10 g) is additionally removed from the filter, the total yield of which comprises 80-85% per 3-nitro-phthalanhydride weight.

15 [0019] 5-nitro-2,3-dihydrophthalazine-1,4-dione (40-50 g) and potassium hydroxide (KOH, 10-15 g) are mixed in distilled water (500-700 ml) to complete dissolution. The solution is heated to 60-75°C, hydrazine hydrate ($N_2H_4 \cdot H_2O$, 12-15 ml) and Ni-Rene catalyst (2-5 g) are added to the solution. This leads to a violent reaction with self-heating and emission of nitrogen (N_2) and hydrogen (H_2).

[0020] When temperature reaches 85-95°C, the reaction mixture is cooled by adding distilled water. After 20-40 min, the additional catalyst (2-5 g) is fractionally added to the solution excluding the possibility of an extremely violent reaction. When self-heating is terminated, additional amounts (5-10 g) of the catalyst are added.

20 [0021] After completing the reaction, the solution is decanted from the precipitated catalyst, filtered, and 5-amino-2,3-dihydrophthalazine-1,4-dione ($C_8H_7N_3O_2$) is precipitated by acidification of the reaction mixture with an aqueous solution of hydrochloric acid (HCl) or a mixture of hydrochloric and acetic acids.

[0022] The precipitate is filtered, washed with distilled water, and dried.

[0023] The product yield per 5-nitro-2,3-dihydrophthalazine-1,4-dione weight is 82-84 %.

25 [0024] In the final stage, 5-amino-2,3-dihydrophthalazine-1, 4-dione (30-40 g) is dissolved in an aqueous solution of sodium hydroxide (10-15 g NaOH per 300-500 ml H_2O) at a temperature of 20-80°C. The solution is filtered, mixed with a lower alcohol (ROH. 1500-2000 ml), e.g., isopropyl alcohol (iso- C_3H_7OH) and held at 20-25°C for 2-3 hours, isolating the target product ($C_8H_6N_3NaO_2$).

[0025] Other lower alcohols or a ketone can also be used.

[0026] The target product yield per 5-amino-2,3-dihydrophthalazine-1,4-dione weight is 85-90 %.

30 [0027] The obtained medicinal preparation is characterized by informative UV spectra in the field of 220-400 nm, taken in concentration of 20 $\mu g/ml$ in various solvents: water, 0.01 M solution of hydrochloric acid, 95 % alcohol, and 0.1 M sodium hydroxide.

INDUSTRIAL APPLICABILITY

35 [0028] Clinical tests showed that administration of the medicinal preparation 5-amino-2,3-dihydrophthalazine-1,4-dione sodium salt to patients with impaired cellular immunity, e.g., in case of malignant neoplasms, causes activation of macrophages, which is evident by release by them of tumor necrosis factor (TNF), interleukins, and other acute-phase proteins. Besides this, the agent initiates specific reactions of T-lymphocytes.

40 [0029] In case of inflammatory diseases the medicinal preparation selectively (for 4-8 hours) inactivates macrophages, decreasing the contents of TNF and acute-phase proteins, that leads to attenuation of intoxication symptoms. At the same time 5-amino-2,3-dihydrophthalazine-1,4-dione sodium salt enhances super-oxidizing function and phagocytic activity of neutrophilic granulocytes, stimulating thus the microbicidal system in cells, and attenuating inflammation process.

45 [0030] These results are confirmed by laboratory analyses on patients, by blood tests, that characterize immunological parameters of the leukocytic and lymphocytic systems.

50 [0031] The medicinal preparation introduced into organism is practically completely eliminated therefrom with expired air and urine in 20-60 min. This preparation in a wide range of doses (20-1500 mg) does not cause side effects and allergic reactions, and its efficiency is similar or even higher than that of prior art immunomodulator, that allows to interchange these medicinal preparations during long-term therapy, in order to prevent the development of patient's tolerance.

[0032] The medicinal preparation can be used in form of powder for injections or tablets for peroral administration.

[0033] Clinical efficiency of the developed medicinal preparation is confirmed by the following observations.

55 Example No.1

[0034] Patient S. of 58 years old.

[0035] Was hospitalized on February 2, 2000 with complaints of fatigability, long-continued cough, and transient

fever (presumably residual symptoms after influenza she had on January 15-27, 2000).

[0036] Examination of the patient revealed sub febrile temperature, dry cough, and rales in the lungs.

[0037] The patient was treated with 5-amino-2,3-dimorphthalazine-1,4-dione sodium salt (further Tamerit).

[0038] Tamerit was injected in a single dose of 300 mg in 2 ml of distilled water for 5 days and then given perorally (powder or tablets) in a dose of 100 mg, 2 times a day, 1 hour after meals.

[0039] Three days after beginning of the therapy the state of the patient was improved, cough disappeared, and temperature returned to normal.

[0040] The patient was considered to be in a satisfactory state in 10 days after beginning of the therapy.

[0041] Results of laboratory analyses are shown in Table 1.

Example No.2

[0042] Patient I., 68 years old.

[0043] Was hospitalized with complaints of difficult urination and urges to urinate.

[0044] Ultrasound examination revealed hypertrophy of the prostate.

[0045] Diagnosis: stage II prostatic adenoma.

[0046] Two courses of therapy with 2-amino-1,2,3,4-tetrahydrophthalazine-1,4-dione sodium salt dihydrate were performed by injections for 20 and 15 injections, respectively, with a 30-day interval between the injections. Doses of the preparation were from 100 to 500 mg in 1-5 ml of distilled water correspondingly.

[0047] The size of adenoma decreased after the first course of 20 injections, but remained without further positive dynamic after the second course of final 15 injections.

[0048] The patient state was considered to be unstable.

[0049] The patient was additionally daily injected with Tamerit - 10 injections in a single dose of 200 mg in 2 ml of distilled water, 1 injection daily.

[0050] The state of this patient was improved, urination was normalized.

[0051] The results of laboratory analyses are shown in Table 2.

Example No.3

[0052] Patient G., 42 years old.

[0053] Was hospitalized with diagnosis of erysipelas of the left forearm, edema, and exacerbation of psoriasis (temperature at hospitalization was 39.9°C).

[0054] Before hospitalization, the symptoms of psoriasis were controlled by ointments.

[0055] Tamerit was injected daily in a single dose of 200 mg in 2 ml water.

[0056] Edema and hyperemia of the left forelimb disappeared in 4 days after beginning of the therapy.

[0057] The patient received injections of Tamerit in a single dose of 100 mg in 1 ml water for the next 5 days.

[0058] The patient was considered to be in a satisfactory state. The state of the skin in the face and hands was improved.

[0059] The patient was prescribed to take Tamerit perorally in a single dose of 100 mg (1 tablet) 2-3 times a day for 7-10 days.

[0060] The results of the laboratory analyses are shown in Table 3.

TABLE 1.

Laboratory Analyses of Patient S.		
Parameter	Before therapy	After therapy
Routine blood test		
Hemoglobin, g/liter	100	147
Erythrocytes, $\cdot 10^{12}$ /liter	3.9	5.0
Color index	0.85	0.9
Leukocytes, $\cdot 10^9$ /liter	4.0	5.5
Eosinophils, %	2.9	3.0
Neutrophils:		
Stab, %	6.0	6.0
Segmented, %	69.5	74.0
Lymphocytes, %	20.5	23.0

TABLE 1. (continued)

Laboratory Analyses of Patient S.		
Parameter	Before therapy	After therapy
Routine blood test		
Monocytes, %	5.5	6.0
ESR, mm/h	5	13.0
Biochemical blood test		
Iron, mg/dl	50.0	51.5
Glucose, mmol/liter	4.2	5.3
Urea, mg/dl	19.0	16.5
Uric acid, mg/dl	5.3	7.1
Albumin, g/liter	37.5	50.0
Protein, g/liter	76.5	71.5
Cholesterol, mg/dl	176.6	154.0
Triglycerides, mg/dl	212.1	195.0
Total bilirubin, mg/dl	0.35	0.4
Creatinine, mg/dl	0.6	0.45
Alkaline phosphatase, U/liter	198.0	212.0
Creatine kinase, U/liter	32.8	34.0
Aspartate transaminase, U/l	33.0	29.5
Alanine transaminase, U/liter	85.0	70.7
g-Glutamyltransferase, U/liter	94.5	93.0
Lactate dehydrogenase, U/liter	201.0	207.5
Cellular and humoral immunity tests		
Immunoglobulin A, g/liter	2.15	2.20
Immunoglobulin M, g/liter	2.0	2.21
Immunoglobulin G, g/liter	11.0	12.4
T-lymphocytes, %	52.0	67.0
B-lymphocytes, %	18.0	24.5
Latex phagocytosis, %	60.0	76.2
TNF	15.0	22.5
T-helpers, %	26.0	29.5
T-suppressors, %	21.0	23.5

TABLE 2.

Laboratory Analyses of Patient I.			
Parameter	Before therapy	After injections	
		2-amino	5-amino
Routine blood test			
Hemoglobin, g/liter	120	130	135
Erythrocytes, *10 ¹² /liter	5.0	5.20	5.25
Color index	0.9	0.95	0.95
Leukocytes, *10 ⁹ /liter	6.50	6.20	6.21
Eosinophils, %	4.0	3.80	3.85
Neutrophils:			
Stab, %	6.5	5.5	6.0
Segmented, %	60.0	64.3	70.0

TABLE 2. (continued)

Laboratory Analyses of Patient I.			
Parameter	Before therapy	After injections	
		2-amino	5-amino
Routine blood test			
Lymphocytes, %	12.0	12.5	14.6
Monocytes, %	3.0	2.5	2.5
ESR, mm/h	357	17.0	10
Biochemical blood test			
Iron, mg/dl	116.4	122.5	123
Glucose, mmol/liter	5.0	5.4	6.0
Urea, mg/dl	10.1	16.2	15.9
Uric acid, mg/dl	2.7	5.3	6.3
Albumin, g/liter	38.8	51.6	60.5
Protein, g/liter	71.3	69.0	65.5
Cholesterol, mg/dl	204.2	195.7	176.4
Triglycerides, mg/dl	160.1	135.0	128.0
Total bilirubin, mg/dl	0.3	0.52	0.55
Creatinine, mg/dl	0.47	0.38	0.34
Alkaline phosphatase, U/liter	212.7	202.0	207.2
Creatine kinase, U/liter	34.0	37.5	38.5
Aspartate transaminase, U/l	35.5	29.9	28.6
Alanine transaminase, U/liter	87.7	72.5	68.2
g-Glutamyltransferase, U/liter	105.5	97.5	92.4
Lactate dehydrogenase, U/liter	204.7	210.0	214.5
Cellular and humoral immunity tests			
Immunoglobulin A, g/liter	2.07	2.33	2.41
Immunoglobulin M, g/liter	1.92	2.07	2.11
Immunoglobulin G, g/liter	11.1	12.3	12.6
T-lymphocytes, %	54.5	66.0	71.6
B-lymphocytes, %	15.5	23.8	29.1
Latex phagocytosis, %	44.0	65.3	83.0
TNF	15.5	20.9	23.0
T-helpers, %	27.2	30.7	32.4
T-suppressors, %	19.7	23.5	24.0

TABLE 3.

Laboratory Analyses of Patient G		
Parameter	Before therapy	After therapy
Routine blood test		
Hemoglobin, g/liter	122	148
Erythrocytes, $\cdot 10^{12}$ /liter	6.2	6.9
Color index	0.92	0.98
Leukocytes, $\cdot 10^9$ /liter	7.0	6.2
Eosinophils, %	4.7	4.0
Neutrophils:		
Stab, %	6.0	5.7

TABLE 3. (continued)

Laboratory Analyses of Patient G		
Parameter	Before therapy	After therapy
Routine blood test		
Segmented, %	62.0	65.5
Lymphocytes, %	19.9	26.3
Monocytes, %	2,7	2.0
ESR, mm/h	37	16.0
Biochemical blood test		
Iron, mg/dl	114.4	125.5
Glucose, mmol/liter	5.4	5.9
Urea, mg/dl	12.9	11.9
Uric acid, mg/dl	3.2	4.15
Albumin, g/liter	46.5	57.1
Protein, g/liter	76.2	77.7
Cholesterol, mg/dl	209.0	200.6
Triglycerides, mg/dl	167.0	172.2
Total bilirubin, mg/dl	0.85	0.65
Creatinine, mg/dl	0.90	0.85
Alkaline pliosphatase, U/liter	209.0	221.0
Creatine kinase, U/liter	31.5	37.5
Aspartate transaminase, U/l	30.5	27.3
Alanine transaminase, U/liter	80.1	58.5
g-Glutamyltransferase, U/liter	93.1	95.2
Lactate dehydrogenase, U/liter	210.5	229.6
Cellular and humoral immunity tests		
Immunoglobulin A, g/liter	2,20	2,47
Immunoglobulin M, g/liter	1,80	2,31
Immunoglobulin G, g/liter	13,0	13,7
T-lymphocytes, %	57,7	60,3
B-lymphocytes, %	26,2	25,0
Latex phagocytosis, %	60,6	83,4
TNF	16,5	24,4
T-helpers, %	19,0	31,2
T-suppressors, %	18,2	20,1

Claims

1. A medicinal preparation having immunomodulatory, antiinflammatory and antioxidant properties, **characterized in that** the preparation is 5-amino-2,3-dihydrophthalazine-1,4-dione sodium salt.
2. A method for manufacturing of medicinal preparation 5-amino-2,3-dihydrophthalazine-1,4-dione sodium salt including reduction of the product by hydrazine hydrate in presence of a skeletal nickel catalyst, **characterized in that**, firstly, 5-nitro-2,3-dihydrophthalazine-1,4-dione is formed by interaction of 3-nitro-phmalanhydride with hydrazine hydrate in acetic acid at 90-120°C, after reduction of which by hydrazine hydrate in a water-alkaline medium in presence of a skeletal nickel catalyst, 5-amino-2,3-dihydrophthalazine-1,4-dione is isolated, which is treated with sodium hydroxide in presence of a lower alcohol or a ketone at 20-80°C to obtain the target product.

Amended claims under Art. 19.1 PCT

1. Application of 5-amino-2,3-dihydrophthalazine-1,4-dione sodium salt as a medicinal preparation having immunomodulatory, antiinflammatory and antioxidant properties.

2. A method for manufacturing of medicinal preparation 5-amino-2,3-dihydrophthalazine-1,4-dione sodium salt including reduction of the product by hydrazine hydrate in presence of a skeletal nickel catalyst, **characterized in that**, firstly, 5-nitro-2,3-dihydrophthalazine-1,4-dione is formed by interaction of 3-nitro-phthalanhydride with hydrazine hydrate in acetic acid at 90-120°C, after reduction of which by hydrazine hydrate in a water-alkaline medium in presence of a skeletal nickel catalyst, 5-amino-2,3-dihydrophthalazine-1,4-dione is isolated, which is then treated with sodium hydroxide with addition of a lower alcohol or a ketone at 20-80°C to obtain the target product.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/RU 01/00086

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K 31/502, C07D 237/32, A61P 37/02, 39/06, 29/00

International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K 31/13, 31/50, 31/502, C07D 237/32, A61P 29/00, 37/02, 39/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	SU 130903 A (E.P. KRYSIN et al.) 1960	
X	The description, pages 1, 2	1
A		2
A	RU 2113222 C1 (ZAKRYTOE AKTSIONERNOE OBSHESTVO "TSENTR SOVREMENNOI MEDITSINY " MEDIKOR") 20 June 1998 (20.06.98)	1
A	SU 656516 A (DZE BUTS KOMPANY LIMITED) 05 April 1979 (05.04.79)	2
A	US 4226993 A (MILES LABORATORIES, INC.) 7 October 1980 (07.10.80)	2

☐ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

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Date of the actual completion of the international search
03 May 2001 (03.05.01)Date of mailing of the international search report
10 May 2001 (10.05.01)Name and mailing address of the
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